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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/603,800	06/26/2003	Junji Hamuro	238027US0CONT	7806

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 03/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/603,800	HAMURO ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-31 and 33-42* is/are pending in the application.

4a) Of the above claim(s) *24-26 and 40-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-23, 27-31 and 33-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 1/5/06 was entered.

Amended claims 21-31, 33-39 and new claims 40-42 are pending in the present application.

Applicants elected previously with traverse the following species: (a) macrophages as a cell species; (b) N,N'-diacylcystine as a species of a substance; and (c) corneal epithelium as a species of an organ, in the reply filed on 12/23/04.

Claims 24-26 and 40-42 are withdrawn from further consideration because they are directed to non-elected species.

Accordingly, amended claims 21-23, 27-31 and 33-39 are examined on the merits herein with the above elected species.

Response to Amendment

The rejection under 35 U.S.C. 112, first paragraph, was withdrawn in light of Applicant's amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-23, 27-31 and 33-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamuro et al. (EP 1 004 302 A2, IDS) in view of Hegde et al. (Invest. Ophthalmol. Vis. Sci. 41:3341-3347, 2000) and Isseroff et al. (US 2002/0039788 A1). ***This is a new ground of rejection.***

Hamuro et al already disclose N, N'-diacetylcystine [$(NAC)_2$] to be a substance having the activity of reducing the content of reductive glutathione in the macrophages (page 9, paragraphs 49-51; page 5, paragraph 21), and that this immunomodulator can be included in a drug, a food (e.g., food for medical care, a health food or a special sanitary food, a toothpaste, a chewing gum and the like), a nutrient (e.g., vitamin and calcium preparations) and an infusion such as a high calory infusion, a physiological saline solution and blood preparations (see abstract; page 2, paragraphs 1-2; page 3, paragraph 10; page 6, paragraph 22). Please not that a physiological saline solution, a high calory infusion, a chewing gum is considered to be a pharmaceutically acceptable carrier. Hamuro et al further teach the immunomodulator is useful as an

immunosuppressant against human immunological diseases such as hepatic cirrhosis, hepatitis, diabetes, gastrointestinal inflammatory diseases such as inflammatory bowel diseases (e.g., ulcerative colitis and Crohn disease), autoimmunological diseases and allergic diseases such as hypersensitive interstitial pneumonia, pulmonary fibrosis, chronic rheumatoid arthritis, asthma and cutaneous atopy (see abstract). Hamuro et al also disclose that the immunomodulator can be applied not only to patients suffering from attacked or chronic diseases but also to high-risk persons suffering from adult diseases (page 10, last sentence of paragraph 57). The dose of the substance having an activity of changing the content of reductive glutathione as an active ingredient, $(NAC)_2$ for this instance, is selected depending on the conditions of the patients or the like to which the substance is administered or the use purpose, including the dosage between 1 and 5,000 mg (oral drug), preferably between 10 and 500 mg/day, which is within the recited dose ranging from 1 mg to 10 g (page 10, top of paragraph 54). Non-limited examples showed that $(NAC)_2$ was administered intraperitoneally at 20 ug/0.5ml/h each for 20 h in mice on day 1 and day 2 to induce oxidative macrophages (example 9), and that the administration of $(NAC)_2$ inhibits delayed type hypersensitivity reaction to ovalbumin (example 10) as well as inhibition of spontaneous inflammatory bowel diseases in γc knockout mice having intestinal inflammation similar to that of humans (example 13) and suppression of joint swelling in a rat adjuvant-induced arthritis (example 19).

Hamuro et al do not teach specifically the use of N, N'-diacetylcystine [$(NAC)_2$] to suppress a rejection to a minor antigen in any allograft, particularly a corneal epithelium

allograft in a recipient in need thereof, even though they teach that $(NAC)_2$ is useful as **an immunosuppressant** against various human immunological diseases such as hepatic cirrhosis, hepatitis, diabetes, gastrointestinal inflammatory diseases such as inflammatory bowel diseases (e.g., ulcerative colitis and Crohn disease), autoimmunological diseases and allergic diseases such as hypersensitive interstitial pneumonia, pulmonary fibrosis, chronic rheumatoid arthritis, asthma and cutaneous atopy, and particularly $(NAC)_2$ has been shown to inhibit a delayed type hypersensitivity reaction to ovalbumin (example 10) in a mouse model.

At the effective filing date of the present application (12/26/00) Hegde et al already taught that the relevant immune response during corneal allograft rejection is a donor-specific delayed type hypersensitivity (DTH) reaction (see at least the abstract). Hegde et al further teach that except in high risk cases, neither HLA typing nor systemic immunosuppression is performed routinely and although typical 2-year survival rates for initial grafts onto avascular graft beds are in excess 90%, approximately 4000 corneal grafts fail each year in the United States because of immunological rejection (page 3341, col. 1, first paragraph).

Isseroff et al also taught methods of treating a damaged or diseased ocular surface by applying a corneal epithelial composite graft to the damaged or diseased ocular surface, wherein the graft comprises a plurality of corneal epithelial cells, including autologous or allogeneic cells (see at least paragraphs 18-20, 35 and 47-48). Isseroff et al further disclose that although patients 13 and 14 had successful allografts

complications associated with Cyclosporin A resulted in either the decrease or temporarily discontinuation of the immunosuppressant drug (bottom of paragraph 47).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Hamuro et al by using N, N'-diacetylcystine [$(NAC)_2$] as an immunosuppressant to suppress a rejection to a minor antigen in an allograft, including a corneal epithelium allograft in a recipient in need thereof in light of the teachings of Hegde et al. and Isseroff et al.

An ordinary skilled artisan would have been motivated to carry out the above modification for the following reasons. Firstly, $(NAC)_2$ is taught to be useful as an immunosuppressant against various human inflammatory immunological diseases by Hamuro et al., and an allograft rejection is considered to be an inflammatory immunological disease. Secondly, it has been shown to inhibit successfully a delayed type hypersensitivity reaction *in vivo* and the DTH reaction has been demonstrated by Hegde et al to be the relevant immune response responsible for corneal allograft rejection. Thirdly, due to the apparent non-toxicity of $(NAC)_2$ because of its inclusion in food (e.g., food for medical care, a health food or a special sanitary food, a toothpaste, a chewing gum and the like), a nutrient (e.g., vitamin and calcium preparations) and an infusion such as a high calory infusion, the use of $(NAC)_2$ would be free of complications associated with conventional immunosuppressant drugs such as Cyclosporin A as already noted by both Hegde et al. an Isseroff et al. Fourthly, the use of $(NAC)_2$ as a complication-free immunosuppressant would reduce the rejection of corneal epithelial allografts in a patient in need thereof.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Hamuro et al., Hegde et al. and Isseroff et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Celine Qian, Ph.D., may be reached at (571) 272-0777, or SPE, Dave Nguyen, at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QUANG NGUYEN, PH.D
PATENT EXAMINER